T-Cell Activation

Introduction

The mature naive T cell, set either as $CD8^+$ or $CD4^+$, now needs to be **activated** to do anything. Activation happens in secondary lymphoid organs such as the spleen or lymph nodes, where those APCs we encountered in #5: *APCs and MHCs* come back from the inflamed tissue to offer up antigens for inspection. The T cells then screen these antigens, find out what they are, and initiate the adaptive immune response.

The **primary stimulus** is the [MHC of APC] + [TCR of T cell] + [either CD4 or CD8] + [CD3]. All four components need to be present for the stimulus to work. Remember, MHC-1 goes with CD8 and MHC-2 goes with CD4. The **costimulatory signal** is the stabilization by provided by the interaction of B7 on the APC and CD28 on the T cell (the same thing we saw in activation of B cells), and by a third stimulus similar to CD40 (but is left nameless here by design). **Cytokines**, especially IL-2, help the naive T cell complete the maturation process. In the activation of B cells, a mature naive B cell was supervised by a mature T cell, and that mature T cell sent proliferation cytokines to the naive B cell. In the activation of T cells, the naive T cell **receives cytokines** from the **professional APC**. It's not that cytokines come from one type of cell or another; it's that cytokines come **from the professional to the naive.** And in the case of T-cell activation, the APC sends different cytokines based on exposure to different pathogens. This last fact will play an important role in determining whether an activated T cell goes down the T_H1 or T_H2 pathway.

$CD4^+$ vs. $CD8^+$ Activation

CD8 cytotoxic T cells (Tc, $CD8^+$, cytotoxic T cell all mean the same thing) require a **primary** stimulus of the TCR combining with the **MHC-1-Antigen** complex, and a **costimulatory** stimulus of the B7 receptor on the APC with the CD28 receptor on the T-cell. CD8 cytotoxic cells also need **cytokine stimulation** (IL-2) from **T-helper** ($CD4^+$) cells to ultimately differentiate into the fully cytotoxic T lymphocytes (mediated by the IL-2 receptor on the T cell).

CD4 T-helper cells (T_H, $CD4^+$, T-helper all mean the same thing) also require a **primary stimulus** of the TCR combining with the **MHC-2-antigen** complex, and a **costimulatory** stimulus of the B7 receptor on the APC with the CD28 receptor on the T cell. $CD4^+$ T-helper cells also need **cytokine stimulation** from **"it's complicated"** cells to ultimately differentiate into one of many lines. "It's complicated" is the next section . . . read on.

CD4 T-Helper Cell Activation Is Complicated = "It's Complicated"

CD4 T-helper cells receive the signal from APCs and send out the final marching orders for all **effector mechanisms** of the adaptive immune system. For that to happen, the CD4 T-helper cell needs to start at a point where it can hear any message, interpret it, and then send the right message to the right cells to start the fight. To "hear any message" it must be naive and able to respond to cytokines.

T_H0 T cells can "hear any message." They're able to ensure that the APC is an APC with the MHC-TCR and B7-CD28 link. This sets the T_H0 cell to listen. The APC then sends out local cytokines based on the pathogen it's brought with it, which induces a change in the function of the T_H0 T cell.

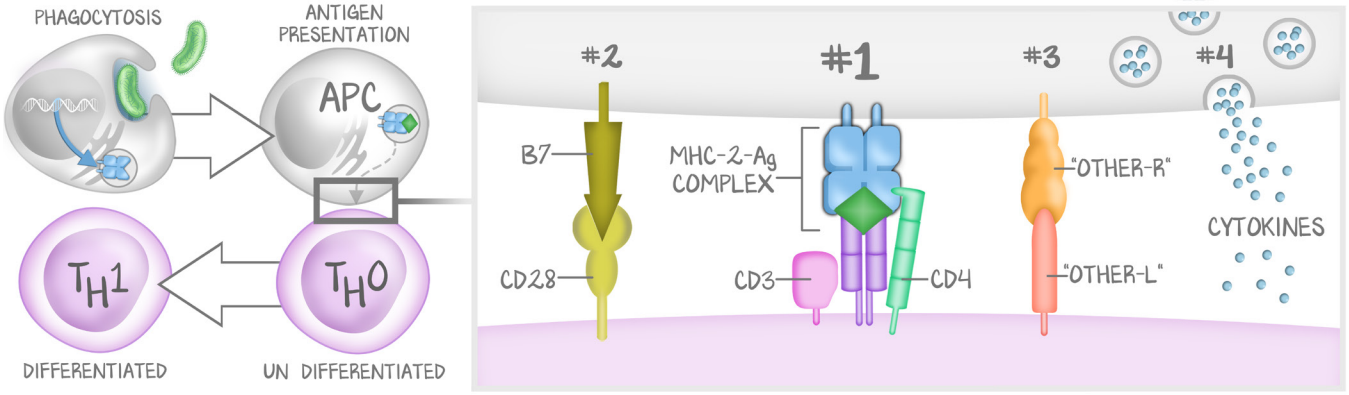

Figure 10.1: Phagocytosis to Presentation
The professional APC uses phagocytosis to engulf a pathogen or antigen. It degrades it in the lysosome. Then it uses MHC-2-Ag complex as the presenting signal. The TCR on a naive T_H0 cell identifies the MHC-2-Ag complex. Costimulatory signals from the professional APC to the naive T-helper cell determine the outcome of differentiation, that is, whether the T_H0 cell will become T_H1 or T_H2.

If an APC has brought back information on an **intracellular pathogen**, it releases **IL-12** and induces the T_H0 to become **T_H1**. T_H1 is named T_H1 because it was the first found. It secretes **interferon-γ.** IFN-γ self-promotes differentiation to T_H1, inhibits differentiation to T_H2, and activates **macrophages** and B-cell **IgG class switching**. The T_H1 turns on the things that kill via phagocytosis. Because intracellular pathogens are hiding in host cells, T_H1 cells also secrete **IL-2** which recruits cytotoxic CD8 lymphocytes. These CD8 cells are activated by associating their TCR with the MHC-1 of affected cells, but the T_H1 adaptive response enhances their activity.

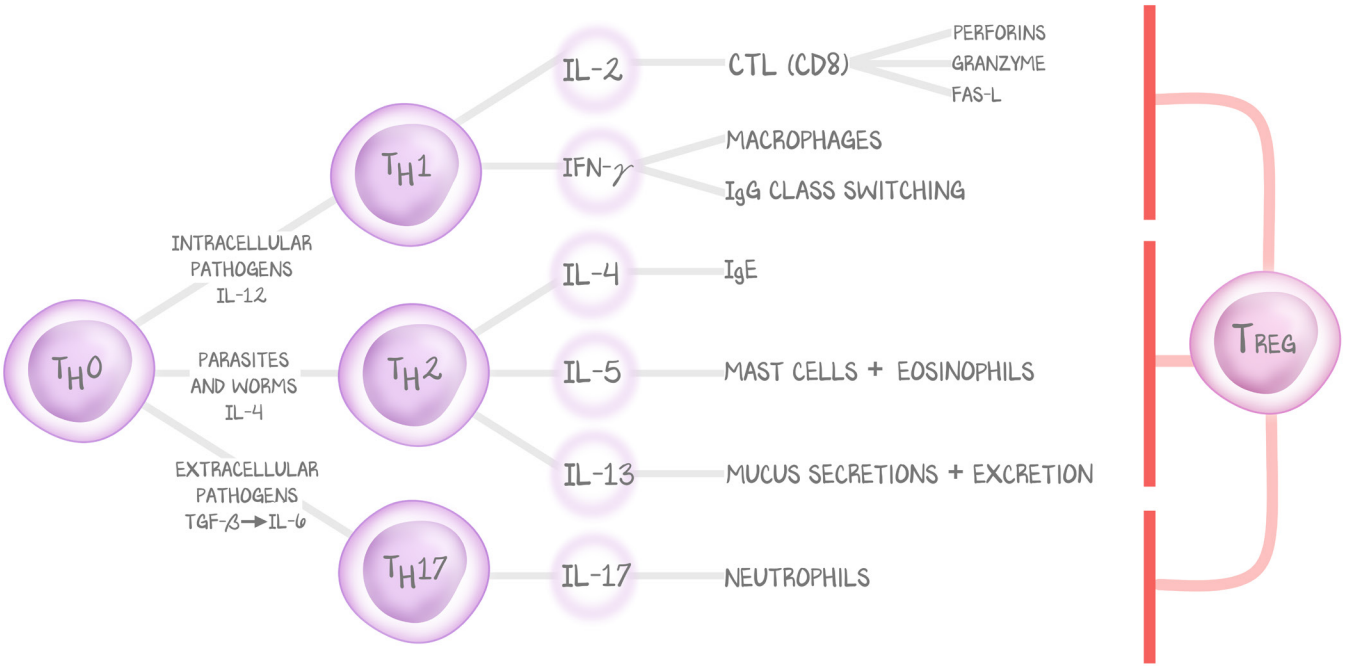

Figure 10.2: Fate of T-Helper Cells
The T_H0 cell will differentiate based on the antigen carried by the incoming APC. There will of course be overlap. Most clearly, neutrophils and macrophages phagocytose bacteria. Because this is so much to memorize, learn these pathways as three separate, discrete, nonoverlapping pathways.

If an APC has brought back something from a **parasitic infection** (worms, helminths that are too big to phagocytose), the APC releases **IL-4,** inducing the T_H0 to become **T_H2**. T_H2 was named such because it was the second type of T cell found. T_H2 produces a bunch of interleukins (IL-4, 5, 10, and 13). The main cytokine is IL-4 which keeps T_H2 going, drives B cells to switch to IgE, and inhibits T_H0 differentiation to T_H1. IL-5 recruits eosinophils and increases mucosal secretion of IgA. Parasites are big, and are usually in mucosal regions (like the gut or lungs), and so they need to be expelled. IgE, mast cells, and eosinophils all help to fight the same parasitic invaders. They help to cause the release of histamine in the mucosal linings and cause those areas, like the gut, to empty.

If the APC has brought back something from an **extracellular bacteria** or **fungus**, it releases **IL-6 and TGF-β**, inducing the T_H0 to become **T_H17**. T_H17 (the only one named correctly for its function) is called that because it produces **IL-17**, which helps to summon more **neutrophils** to the site of infection and induces the epithelium to secrete antimicrobial chemokines.

Ultimate Fate of T Cells

All of these cells undergo clonal expansion when they activate. That is, a lot of them get made. A lot of them get made so we can send overwhelming numbers of "soldiers" to fight whatever pathogen is there. And since we know the exact pathogen (at least the exact antigen), it makes sense to make a lot of very specific T cells that fight that pathogen, for as long as it is around.

95% of the T cells we've discussed are **effector T cells**. Effector cells are those immune cells that can instigate an immune response without further differentiation. These are **short-lived** and **antigen-specific** lymphocytes. We called B cells that served this same purpose plasma cells. T cells don't have a special name.

Their life is shortened by **T-regulatory (T_{reg}) cells**, a special type of CD4 T helper that downregulates the activity of effector T cells. They exist so the inflammatory response isn't perpetuated forever. When the source of inflammation is cleared (the pathogen destroyed), the inflammation is turned off. The only thing worth learning about T_{regs} (as their mechanism of generation and mechanism of function is poorly understood) is that they are identified by the surface marker **$CD25^+$**. The only time you will see $CD25^+$ is in relation to T_{regs}.

5% of the T cells we've discussed become **memory T cells**. These are specialized T cells that **are long-lived** and **antigen-specific**. They lie dormant and can reactivate with ease upon re-exposure to the same antigen. Their response to antigen exposure this second time is faster and more robust than the first time.